

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 29/02, 37/00, A61N 1/30	A1	(11) International Publication Number: WO 95/05866 (43) International Publication Date: 2 March 1995 (02.03.95)
(21) International Application Number: PCT/US94/09590 (22) International Filing Date: 26 August 1994 (26.08.94) (30) Priority Data: 08/113,273 27 August 1993 (27.08.93) US (71) Applicant: CORTRAK MEDICAL INC. [US/US]; 2660 Patton Road, Roseville, MN 55113 (US). (72) Inventors: SHAPLAND, James, E.; 4322 Rustic Place, Shoreview, MN 55126 (US). KNUDSON, Mark, B.; 1309 West Royal Oaks Drive, Shoreview, MN 55126 (US). SHIMADA, Jin; 1497 West Idaho Avenue, Falcon Heights, MN 55108 (US). RACCHINI, Joel, R.; 4221 West 44th Street, Edina, MN 55424 (US). (74) Agent: BRUESS, Steven, C.; Merchant, Gould, Smith, Edell, Welter & Schmidt, 3100 Norwest Center, 90 South Seventh Street, Minneapolis, MN 55402 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD). Published <i>With international search report.</i>
(54) Title: SIMULTANEOUS ANGIOPLASTY AND DRUG DELIVERY		
(57) Abstract <p>A method of simultaneous angioplasty and drug delivery to a localized portion of coronary or peripheral arteries or any other type of body passage that has a stricture. The invention contemplates positioning a drug delivery device in a body passageway and then selectively introducing a selected drug so that the device is expanded in order to dilate the passage and then simultaneously causing the drug to be transported across a drug transport wall of the device for direct contact with the passageway wall. A more specific aspect of the present invention involves treating a dilated vessel in the area of a stenotic lesion with a fixative or other drug to render the vessel biologically inert and to form a biological stent or prevent restenosis using specifically selected drugs.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

SIMULTANEOUS ANGIOPLASTY AND DRUG DELIVERY

BACKGROUND OF THE INVENTION1. Field of the Invention

5 The present invention relates generally to a simultaneous angioplasty and drug delivery method for and more particularly, to a method for simultaneously performing angioplasty and selectively and locally delivering a drug to internal body tissue.

2. Description of the Prior Art

10 Many techniques currently exist for delivering drugs or other medicaments to body tissue. These include, among possible others, oral administration, 15 injection directly into body tissue such as through an intramuscular injection or the like, topical or transcutaneous administration where the drug is passively absorbed, or caused to pass, into or across the skin or other surface tissue and intravenous 20 administration which involves introducing a selected drug directly into the blood stream.

 Except for topical or transcutaneous administration, the above drug delivery systems tend to be systemic. In other words, administration of the drug 25 is delivered throughout the body by the blood stream. Although transcutaneous drug delivery systems tend to be localized delivery systems in that the drug is delivered locally to a selected area, such drug delivery systems are also, by definition, limited to application of a 30 drug externally through the patient's skin or other surface tissue. Thus, the above described drug delivery systems are generally not appropriate for the localized treatment of internal body tissue.

 Although many medical situations are 35 satisfactorily treated by the general systemic administration of a drug, there are a great many treatments which could be facilitated and/or improved by the ability to deliver or administer a drug locally to a selected portion of internal body tissue, without

appreciably affecting the surrounding tissue.

One example is the ability to treat the dilated vessel in percutaneous transluminal coronary angioplasty (PTCA), and thus limit or prevent restenosis. In PTCA, catheters are inserted into the cardiovascular system under local anesthesia and an expandable balloon portion is then inflated to compress the atherosclerosis and dilate the lumen of the artery. Despite the general success of such PTCA procedures, high restenosis rates (reported to be as high as 47%) continue to be a major problem. Various techniques have been tried to treat stenosed vessels including the use of lasers, application of heat and the use of intravascular stents. However, many of these are still under investigation with mixed results, while others have generally not been successful. The ability to administer a drug locally to the dilated portion of the artery in PTCA procedures, without significantly affecting other tissues, would greatly enhance the ability to address the restenosis problem.

Accordingly, there is a need in the art for a method and apparatus for delivering a drug selectively and locally to internal body tissue, without significantly affecting other tissue. There is a further need for such a method of simultaneously performing angioplasty and treating the localized internal body tissues to limit restenosis following angioplasty.

30

SUMMARY OF THE INVENTION

In accordance with the present invention, a method is provided for simultaneously performing angioplasty and delivering a drug or combination of drugs selectively and locally to internal body tissue. More specifically, the invention involves a method for simultaneously performing angioplasty and delivering a drug or combination of drugs substantially transversely

to the longitudinal axis of coronary or peripheral arteries or any other type of passage that has a stricture.

In the preferred embodiment, the apparatus for use with the claimed method includes a flexible member adapted for insertion into the body passageway or tissue and a drug delivery means connected with the flexible member for delivering the drug to or through a local area of the passageway wall or tissue. The drug delivery means includes a drug transport wall for engagement with a local area of the passageway wall or tissue and a drug chamber for receiving a selected drug. The chamber is defined in part by the drug transport wall which is constructed of a material that permits selective transport of a drug therethrough, i.e. constructed of at least perforated, permeable, microporous or semipermeable material through which the drug is intended to selectively pass, that is, selectively permeable.

Preferably, in one embodiment the drug delivery means includes a modified catheter balloon or bag. The modified catheter balloon contacts the inner surface of the passageway wall and defines the localized passageway area to or through which the drug is to be administered.

The method of the present invention involves positioning a drug delivery member such as a modified catheter balloon in a body passageway such that the delivery member or balloon traverses the desired localized area of administration. The balloon is then inflated or otherwise expanded to simultaneously dilate the passageway and deliver a drug to the localized area of the passageway. Delivery of the drug involves introducing a selected drug into or through the localized zone or passageway.

A specific application of the apparatus and method of the present invention involves the treatment of a dilated vessel to prevent restenosis following

PTCA. In the preferred embodiment and procedure, this involves administering a fixation solution or fixative to the passageway walls in the localized area.

Administration of the fixative in this area renders the
5 dilated artery biologically inert, resulting in a certain degree of hardening and the production of a biological stent.

Accordingly, it is an object of the present invention is to provide a modified dilation catheter
10 having localized drug delivery capabilities for limiting restenosis and for the delivery of drugs locally to internal body tissues.

This object of the present invention will become apparent with reference to the drawings, the
15 description of the preferred embodiment and method and the appended claims.

DESCRIPTION OF THE DRAWINGS

Figure 1 is a fragmentary view, partially in
20 section, of a first embodiment of the drug delivery apparatus of the present invention in the form of a catheter with a modified dilatation balloon in its deflated state.

Figure 2 is a fragmentary view, partially in
25 section, of the drug delivery apparatus of Figure 1 positioned in a blood vessel with the dilatation balloon in its inflated state.

Figure 3 is a fragmentary view, partially in section, of an alternate design of a drug delivery
30 apparatus in the form of a double balloon catheter positioned in a blood vessel.

Figure 4 is a fragmentary view, partially in section, of a further embodiment of the drug delivery apparatus of the present invention positioned in a blood
35 vessel.

Figure 5 is an enlarged fragmentary view, partially in section, of the embodiment of Figure 4.

Figure 6 is a fragmentary view, partially in section, of the drug delivery apparatus of the present invention positioned in a blood vessel and embodying iontophoresis means to transport the drug across the
5 balloon surface.

Figure 7 is a fragmentary view, partially in section, of the drug delivery apparatus of the present invention positioned in a blood vessel, embodying iontophoresis to transport a drug across the balloon
10 surface where the solution containing the drug is circulated through the balloon.

Figure 8 is a fragmentary view, partially in section, of a still further alternate design of a drug delivery apparatus in accordance with the present
15 invention in the form of a catheter with a drug delivery component to transport a drug to internal body tissue.

Figures 9a and 9b show a cross-section of selectively permeable microporous membrane of the catheter of Figure 8 in cross-section along line 11-11.
20 Figure 9a shows an isotropic (asymmetric) structure. Figure 9b shows a symmetric structure.

Figure 10 is a fragmentary view of a modified iontophoretic embodiment of the drug delivery apparatus shown in Figure 8.

25 Figure 11 is a fragmentary view of a further modified phonophoretic embodiment of the drug delivery apparatus shown in Figure 8.

30 DESCRIPTION OF THE PREFERRED
AND ALTERNATE EMBODIMENTS AND METHODS

Figures 1-7 illustrate the preferred and various alternate designs of the drug delivery apparatus used in accordance with the method of the present invention. In general, this apparatus provides a means
35 and a system for delivering a drug or combination of drugs to or through a localized area of a passageway in order to treat the localized area of the passageway or to treat a localized area of tissue located adjacent to

the passageway, with minimal, if any, undesirable effect on other body tissue. The drug delivery apparatus includes a modified catheter balloon design which can be used in conjunction with existing catheters. The term
5 catheter as used in the present application is intended to broadly include any medical device designed for insertion into a body passageway to permit injection or withdrawal of fluids, to keep a passage open or for any other purpose. It is contemplated that the simultaneous
10 angioplasty and drug delivery method of the present invention has applicability for use with coronary or peripheral arteries or any other type of body passage that has a stricture.

In particular, catheters are commonly used in
15 percutaneous transluminal coronary angioplasty (PTCA) procedures to dilate stenosed blood vessels or arteries. These include so-called over the wire catheters of the type illustrated generally in U.S. Patent No. 4,323,071, and so-called fixed wire catheters of the type
20 illustrated in U.S. Patent No. 4,582,181. These catheters may be modified for use according to the method of the present invention.

In order to illustrate the method aspect of treating a localized area of a passageway according to
25 the present invention, the specific application of the present invention to the reduction of restenosis will be described.

As indicated in the discussion earlier, percutaneous transluminal coronary angioplasty (PTCA)
30 has been demonstrated to be a highly successful procedure for the treatment of atherosclerosis and other diseases and conditions tending to narrow arterial passageways. In normal PTCA procedure, a dilatation catheter is advanced along an artery to the desired
35 position in the arterial system. The catheter includes an inflatable balloon at its distal end and means for inflating the balloon. When the balloon is positioned

so that it traverses or crosses a stenotic lesion, the balloon is inflated to compress the atherosclerosis and expand the artery in a direction generally perpendicular to its wall, thereby dilating the lumen of the artery.

- 5 Following this procedure, the balloon is deflated and the catheter withdrawn.

Despite the generally excellent success of PTCA, relatively high restenosis (the tendency of the dilated artery to close) rates continue to be a major
10 problem. Restenosis can include abrupt reclosure resulting from thrombotic occlusion, vasospasms, or the like as well as the more common occurrence of gradual restenosis.

In accordance with the method of the present
15 invention, a drug referred to as a fixation solution or a fixative is delivered locally to the dilated portion of the vessel to render the vessel wall biologically inert to prevent or reduce reactions that lead to reclosure. Because of the nature of the fixative and
20 its ability to inactivate living cells and render the tissue in which it comes into contact biologically inert, it is essential that such fixative be exposed only to that portion of the arterial wall which has been dilated. A preferred method and apparatus for
25 delivering the fixative locally to the dilated vessel is via a modified catheter balloon in which the balloon catheter that delivers the drug is the same balloon catheter that dilates the vessel, thus combining both functions in one catheter. One embodiment of a modified
30 balloon useful for this approach is illustrated in Figures 1 and 2.

Figure 1 illustrates the distal end of a catheter with the modified catheter balloon in its deflated state. The catheter includes a guide wire 10,
35 an elongated, flexible catheter body 11, a drug delivery means in the form of a balloon 12 positioned on the catheter body 11 near its distal end and a balloon lumen

or passageway 14 extending along the catheter body 11 to the proximal end of the body 11 for inflation and deflation of the balloon 12. In the preferred embodiment, the material from which the balloon 12 is constructed is a permeable or selectively permeable material which is effective to permit transport or passage of the fixative or other drug across the balloon surface as a result of an appropriate driving force.

The structure of the guide wire 10, the catheter body 11 and the balloon lumen 14 is similar to conventional catheter design which is known in the art and an example of which is shown in U.S. Patent No. 4,323,071. The balloon 12 of Figure 1, however, is distinguishable from conventional catheter balloons in that the balloon 12 is constructed from a material which selectively permits the transport or passage of a drug or fixative across the balloon surface.

Figure 2 illustrates the drug delivery apparatus of Figure 1 with the balloon 12 in its inflated state within an arterial vessel in which the vessel walls are indicated by the reference numeral 15. During PTCA procedures, the guide wire 10 is first inserted into the selected artery to a point past the stenotic lesion. The dilatation catheter including the catheter body 11 and balloon 12 is then advanced along the guide wire 10 to the desired position in the arterial system in which the balloon portion 12 traverses or crosses the stenotic lesion. The balloon 12 is then inflated by introducing an inflation fluid through the balloon lumen 14 into the interior chamber 13 of the balloon 12. During inflation, the outer surfaces of the balloon 12 press outwardly against the inner surfaces of the vessel wall 15 to expand or dilate the vessel in the area of the stenotic lesion, thus performing the angioplasty portion of the method.

In accordance with the present invention, and in particular in accordance with the embodiment of

Figures 1 and 2, the balloon 12 is inflated by introducing a fixation or other drug solution through the balloon lumen 14 and into the interior of the balloon portion 12. As a result of at least a portion of the balloon 12 being constructed of a permeable or selectively permeable membrane, the pressure of the drug or fixative within the balloon 12 simultaneously causes the balloon to expand the artery and the drug or fixative to be transported across the walls of the balloon 12 into direct contact with the vessel wall 15.

In the preferred embodiment, it is contemplated that the material from which the balloon of Figures 1 and 2 is constructed will be a selectively permeable membrane material such as microporous ultrafiltration (UF), microfiltration (MF), or dialysis membrane. It is contemplated, however, that various other permeable, microporous or selectively permeable materials may also be used including, without limitation, cellulose, cellulose acetate, polyvinyl chloride, polysulfone, polyacrylonitrile, silicon, polyurethanes, natural and synthetic elastomers. Examples of suitable microporous membranes are polyester, polyolefin, a fluoropolymer, or the like having pore sizes of about 1 micron or smaller and preferably from about 10 Å to 1 micron, with a nominal pore size of about 0.05-1 micron.

It is contemplated that the particular material from which the balloon 12 is constructed will depend to some extent on the specific composition of the fixative or other drug to be delivered as well as the transport or driving pressures which are developed within the balloon chamber 13. In the structure of Figures 1 and 2, the preferred materials from which the balloon 12 is constructed are elastomeric or nonelastomeric materials and the pressure generated within the balloon chamber 13 to result in transport of the drug or fixation solution across the balloon walls is between about 1 and about 90 psi.

A fixative or fixation agent is a compound or composition known in the art as a fixative. A fixative functions, among other things, to kill, penetrate and harden fresh tissues, to set the tissues so that they will not be altered by subsequent biological or other processing and to render the cell constituents insoluble. Fixatives are commonly used for stabilizing and fixing tissue at the moment such tissue is exposed to the fixative so that histologic slides of the tissue can be prepared or the tissue can otherwise be preserved for examination.

The particular fixative or fixation solution as contemplated by the present invention must be able to rapidly penetrate the plaque and vascular tissue of the vessel in the area of the stenotic lesion. It should quickly kill or otherwise preserve the tissue, while hardening the vascular structure. Such fixation maintains the vessel in an "opened" or dilated condition and prevents or substantially reduces reclosure due to vasospasm or other abrupt reclosure mechanisms. Such fixation also retards or stops the biological processes which lead to gradual restenosis. The preferred fixative should also have rapid, specific action in high concentrations, while generally nontoxic actions in lower concentrations.

Current fixatives include:

- Glutaraldehyde
- Formaldehyde
- Acetaldehyde
- Ethyl Alcohol

In accordance with the preferred apparatus and method of the present invention, the fixation solution may contain compounds or drugs to reduce vasomotor action (calcium antagonists) and inflammatory response (steroids) as well as antiplatelet inhibitors and anticoagulants. Calcium antagonists may include materials such as diltiazem HCl, nifedipine and

verapamil HCl, steroids such as dexamethasone and specific nonsteroidal anti-inflammatory agents. Antiplatelet inhibitors and anticoagulants may include materials such as heparin, dipyridamole, papaverine HCl, 5 ethaverine HCl and prostacyclin inhibitors. It is also contemplated that agents inhibiting smooth muscle and fibroblast proliferation which is a primary factor in restenosis, or agents tending to reduce collagen response to injury could also be used either with or 10 without the fixation agent. Fibroblast proliferation inhibiting agents may also be included as well as collagen response reduction agents. It is still further contemplated that compounds which reduce platelet aggregation may also be beneficial to administer with a 15 fixation solution. Also, antitumor or other antimitogenic drugs can be used for prevention of restenosis.

The formulation for the preferred fixative solution in accordance with the present invention is 2% 20 by volume glutaraldehyde in normal saline solution. A second preferred fixative solution includes formalin at a concentration of about 10% in a normal saline solution.

Figure 3 illustrates an alternate design for 25 the catheter balloon utilizing a dual or concentric balloon concept. Specifically, a first, inner balloon 16 is provided which is constructed from a material such as polyethylene which is impermeable. The balloon 16 includes an inner chamber 17 which is connected through 30 the inner balloon lumen 20 to the proximal end of the catheter. The embodiment of Figure 3 is also provided with a second or outer balloon 18 which is generally concentric to the balloon 16 and which extends completely around the balloon 16. This outer balloon 18 35 is constructed from a permeable or selectively permeable material similar to that of the balloon 12 of Figures 1 and 2 and includes a balloon chamber 19 formed between

the outer surface of the balloon 16 and the inner surface of the balloon 18. The chamber 19 is connected through the outer balloon lumen 21 to the proximal end of the catheter. When using the structure of Figure 3, the inflated balloon portion is first inserted into the arterial passageway until it bridges a stenotic lesion in the manner described above and known in the art. During the balloon inflation process contemplated by the structure of Figure 3, the chamber 19 of the outer balloon 18 is first filled with the drug or fixative through the lumen 21. This is followed by inflation of the chamber 17 of the inner balloon 16 with standard inflation medium provided through the lumen 20. As a result of inflation of this inner balloon 16, sufficient pressure is developed against the chamber 19 to simultaneously cause the outer balloon to expand and dilate the artery and to provide the pressure required to drive or transport the fixative through the outer balloon wall 18.

Although the structure of Figure 3 shows a separate lumen 21 for filling the outer balloon chamber 19, it is contemplated that the lumen 21 could be eliminated and the chamber 19 prefilled with the fixative or other drugs. In such a structure, the pressure causing transport of the fixation solution across the balloon wall 18 would be provided solely by inflation of the inner balloon 16.

A further modified balloon structure is illustrated in Figures 4 and 5. The embodiment of Figures 4 and 5 is similar to the embodiment of Figures 1 and 2 except that the balloon structure in Figures 4 and 5 is constructed of two different materials. It will be appreciated that as an alternative, the balloon structure in Figures 4 and 5 can be constructed of a permeable material that is modified to have one or more impermeable portions (i.e., increased thickness). In Figures 4 and 5, the balloon end portions 24 are a

totally impermeable material, while an intermediate portion 22 of the balloon positioned between the end portions 24 is a permeable or semipermeable material. The purpose of this structure is to enable more specific
5 and precise delivery of the fixation solution or other drug desired to be administered. For example, with the end portions 24 constructed of an impermeable material, inadvertent passage of the fixation solution or other drug through such end portions is prevented. In the
10 structure of Figures 4 and 5, the impermeable material may be polyethylene, or polyester or an area of permeable material that is functionally impermeable because of increased thickness or other modification that results in a non-permeable region or regions.

15 In the structure of Figures 4 and 5, the fixative or other drug is permitted to pass from the interior chamber 25 of the balloon only through the balloon portion 22. The material from which the portion 22 is constructed is similar to the material from which
20 the balloon 12 of Figures 1 and 2 and the outer balloon 18 of Figure 3 is constructed.

As a further alternative, the catheters of Figures 1-5 may be coated on their outer surfaces, or at least that portion of the outer surface which is to
25 contact the vessel wall, with hydrogel to improve contact with the vessel wall. The hydrogel so described may also contain the fixative or drug to be delivered where solution passing from the catheter through the hydrogel will dissolve the fixative or drug and
30 transport the fixative or drug to the vessel wall. As a further alternative, drug impregnated hydrogel may be coated on the inside wall of a catheter for similar drug delivery as solution passes through the hydrogel and catheter wall.

35 In the embodiments of Figures 1-5, pressure is the force which is utilized to transport the fixative or other drug from the interior balloon chamber across the

balloon wall to the vessel wall. However, it is contemplated that other transport forces could also be used either with or in lieu of pressure to enhance or otherwise control the speed of drug transport. For example, one method could utilize DMSO as a carrier to transport a fixative or drug through the vessel wall. Other fluid diffusion enhancement compositions include propylene glycol, azone and ionic or non-ionic surfactants.

Another method could utilize iontophoresis technology. Such technology is commonly used in transdermal drug delivery. In general, iontophoresis technology uses an electrical potential or current across a semipermeable barrier to drive ionic fixatives or drugs or drag nonionic fixatives or drugs in an ionic solution. Iontophoresis can be useful in certain applications of the present invention because it facilitates both transport of the fixative or drug across the selectively permeable membrane and enhances tissue penetration.

In the application of iontophoresis, two electrodes, one on each side of the barrier, are utilized to develop the required potential or current flow. In particular, one electrode may be located inside of the catheter in opposed relation to the drug delivery wall of the catheter while the other electrode may be located at a remote site on a patient's skin. In addition to direct current, other wave forms may be utilized (e.g., a series of rectangular waves producing a frequency of 100 Hz or greater).

The embodiment of Figure 6 illustrates a structure utilizing iontophoresis to assist in driving the fixative or other drug across the balloon wall 26 and into contact with the vessel walls 15. In Figure 6, one electrode 28, the catheter electrode, is located on or within the catheter body 11 while the other electrode 31, the body surface electrode, is located on the body

surface or within the body of the patient. In order for iontophoresis techniques to be utilized, the fixative or other drug within the balloon chamber 27 requires specific characteristics. Ideally, such fixative or other drug should have an ionic nature or have other ionic molecules bound to the fixative or the active components of the drug to promote the iontophoretic movement or transport across the balloon wall 26. An electrical current for the iontophoretic process of Figure 6 is produced between the electrodes 28 and 31 by an external power source 30 through the electrical leads 29 and 33, respectively.

During operation of the device of Figure 6, the balloon 26 is first positioned across the stenotic lesion in the manner described above. The balloon interior 27 is then inflated with the fixative through the lumen 23. As the balloon expands, it causes the artery to dilate. This is followed by activating the power supply 30, thereby creating a current between the electrode 28 and the electrode 31 which passes through the balloon wall 26. This current drives or drags the fixative or other drug within the chamber 27 across the wall and into contact with the surrounding vessel wall 15 and vascular tissue. The structure of Figure 6 utilizes both pressure and iontophoresis as the driving force, although, it is contemplated that iontophoresis could be utilized alone.

It is contemplated that iontophoresis by itself, or in combination with a solvent like DMSO as a carrier, could yield fixative or drug transport into or through a vessel wall at pressures less than about 20 mm Hg above normal ambient vessel wall pressure and preferably at less than about 5 mm Hg, thereby avoiding substantial damage to the vessel wall known to occur at higher pressures.

The polarity of the iontophoretic electrodes may be reversed in order to recapture excess fixative or

drug delivered to or through the vessel wall.

A still further embodiment of a drug delivery apparatus in accordance with the present invention is illustrated in Figure 7 which illustrates a modified catheter balloon design having a balloon 44 positioned on catheter body 11 near its distal end. One delivery lumen or passageway 45 extends along the catheter body 11 to the proximal end of the body 11 and a recovery lumen or passageway 46 also extends along the catheter body 11 to the proximal end, said delivery lumen 45 and recovery lumen 46 useful for circulating solution containing a fixative or drug to and from the catheter balloon. The outlets 47 and 48 may be positioned in the balloon to achieve optimal circulation within the balloon. This embodiment may be most useful in delivering drugs which are difficult to dissolve where the delivery solution accordingly is very low in concentration of the drug and easily depleted of such drug. Circulation in this case would be important for continuous delivery over long time periods. This embodiment may be combined with reversing the polarity of the electrodes of iontophoresis in order to remove excess drug after treatment.

In all of the previous embodiments, phonophoresis (sometimes referred to as sonophoresis) can be used as an alternative transport force. Similarly, in the case of the embodiments shown in Figures 8-11, an active transport force--either iontophoresis or phonophoresis--can be employed. Phonophoresis is the use of ultrasonic or high frequency sound waves to transport drugs. As used in the present invention, phonophoresis can be used to transport drugs through the selectively permeable membrane and into the surrounding tissue. For certain therapeutic procedures, phonophoresis has several advantages over iontophoresis, including the ability to achieve greater penetration and to more readily deliver an entire molecule, rather than

an ionically charged form of the drug. All prior applications of phonophoresis have been limited to transdermal delivery of drugs. It has primarily been used to deliver anti-inflammatory agents and local anesthetics through the skin in treating epicondylitis, tendonitis, bursitis and osteoarthritis. It is also well-suited for driving fixatives or drugs across the catheter of this invention to a localized area of coronary or peripheral arteries or any other type of body passage that has a stricture because it facilitates both transport of a fixative or drug across the selectively permeable membrane and enhances tissue penetration. In addition to drug delivery, ultrasound may be advantageously used with the catheter of the present invention based on the increased tissue temperature, tissue hyperemia and increased capillary permeability associated with ultrasound. These actions can enhance intra-tissue drug transport and cellular uptake as well as cause vasodilation/relaxation which may be beneficial in vascular drug applications using catheter embodiments of the type described herein.

When phonophoresis is used with either the vascular delivery embodiment or tissue delivery embodiment of the catheter of the present invention, the cathode electrode 28 of Figure 6 is replaced by an ultrasonic piezoelectric transducer (barium titanate, lead zirconate titanate, or the like), which is connected to the external power source 30 and placed within the catheter opposite the drug delivery wall. The ultrasonic transducer is activated to enhance transport of drugs or fixatives into tissue surrounding the catheter. The diffusion rate of drugs delivered by phonophoresis depends upon the intensity and frequency of the ultrasonic field. Prior transdermal applications of phonophoresis use intensities of .1 to 6 watts/cm and involve direct correlation between the amount of drug diffused and the intensity of the ultrasonic field.

Internal applications (not requiring transdermal delivery) of phonophoresis with the catheter embodiments of the present invention are envisioned to require significantly less intensity to deliver an equal amount of drug. Various frequencies can be used. A frequency of about 1 MHz has been optimally used in transdermal phonophoresis. It is envisioned that approximately 1 MHz or less can be used for internal applications of the catheter embodiments described herein.

According to the present invention, further catheter embodiments are envisioned employing a selectively permeable microporous membrane portion of the drug delivery component, together with an active, non-pressure, transport force for assisting the delivery of the drug to a body tissue (Figures 8, 10, and 11). In these embodiments, the microporous membrane, in conjunction with the active delivery mechanisms, aids in controlling drug transfer from the catheter by minimizing passive diffusion or flow under the slight pressure involved in filling the drug chamber or inflating the balloon to make contact with a vessel wall. However, drug delivery into the tissue under active iontophoretic or phonophoretic delivery will not be inhibited by the membrane.

The microporous material provides more uniform delivery areas, which will provide more uniform drug distribution into the surrounding tissue, will reduce the potential for areas of high current densities during iontophoresis (associated with a few larger pores), and will decrease the potential for tissue damage or breakdown of the membrane material due to high current density.

The numerous micropores will reduce the likelihood that a significant portion of the membrane could become blocked with blood components, secretions, lubricants, or other material. In addition, blood or other secretions will not cross the microporous membrane

and enter the drug chamber during deflation of the balloon. The microporous material will also allow rapid balloon deflation without blood reflux into the catheter, which is an important feature in coronary
5 arterial applications. Finally, the microporous material will allow the use of a neutral or charged membrane surface to promote or control drug transfer and delivery.

As seen in Figures 8, 10, and 11, the
10 selectively permeable membrane has a selectively permeable microporous membrane portion 22'. A schematic structure for the microporous membrane is illustrated in Figures 9a and 9b. Particularly, the selectively
15 permeable microporous membrane can have either an isotropic (asymmetric) or symmetric structure. The pore size of the membrane can vary from about 10 Å to 10,000 Å.

The microporous membrane that satisfies the requirements of the invention can be manufactured in any
20 of several ways, most of which are readily understood by those skilled in the art of manufacturing microfiltration and ultrafiltration membranes. These techniques include, for example:

- 25 1. A phase inversion process in which an appropriate polymer solution is coagulated in a nonsolvent quench bath can be employed.
2. A thermal inversion process can be used whereby a polymer solution or mixture at elevated
30 temperatures can be coagulated by a reduction in temperature, under controlled conditions, to form a microporous membrane.
3. A so-called track-etch process whereby a polymer film is bombarded by protons, electrons, radiation, etc. and then
35 subsequently subjected to a controlled etching can be used as well.
4. A laser may be used to form holes or pores of

the desired size in a polymeric material.

In both processes 1 and 2, conditions can result in either a symmetric or an asymmetric membrane being formed. Either type of membrane can be useful, although a preference may exist for one or the other in a given application. Any post-treatment of the membranes, such as irradiation, chemical grafting, coatings, etc. that would render the membrane more hydrophilic, fouling resistant, form a thin-film composite membrane or impart any other desirable properties would be a possible supplement to the above-mentioned formation processes. These processes are examples of methods that can be used to form a membrane of the desired properties. However, any additional methods that currently exist or that may become apparent that produce the desired membrane properties should also be included in the possible membrane formation mechanisms.

There are several forms or geometries into which these membranes can be made. A flat sheet membrane can be cast and then formed into a balloon shape or cylinder by gluing, sonic welding, etc. Additionally, a hollow fiber membrane can be spun or a tubular membrane cast that can be used as is or processed into a balloon by blow molding or some other balloon-forming process. A third option is to cast the membrane directly into a balloon shape by spin-casting or some other process that allows the desired shape to be achieved. During this processing, a membrane support can be used if desired or required.

One embodiment of the present invention incorporating a selectively permeable microporous membrane is shown in Figure 10. This embodiment includes a drug delivery component in the form of a balloon 12' which contacts the body tissue for drug delivery. The balloon 12' is preferably made of an inelastic material such as polyester, polyolefin, a

fluoropolymer, or the like. Preferably, the balloon 12' includes a selectively permeable microporous membrane portion 22' and a non-permeable section 24' as best shown in Figures 8 and 9. As shown in Figures 10 and 5 11, the drug delivery component is formed proximate the distal end of the catheter and includes an active, non-pressure transport force such as iontophoresis (Figure 10) or phonophoresis (Figure 11).

One embodiment of a drug delivery apparatus 10 having a selectively permeable microporous membrane, together with an iontophoretic driving force, is shown in Figure 10. In Figure 10, the drug delivery apparatus includes an electrode 28 within the balloon 12'. Drug is delivered to the balloon 12' through a drug input 15 lumen 45' and an input port 47'. The embodiment shown in Figure 10 further includes a drug recovery lumen 46' in fluid communication with the drug delivery component 49 through drug recovery port 48'. The embodiment in Figure 10 further shows a conductor lumen 27 for the 20 electrode wire/conductor 29'. The conductor 29' could alternately be inserted along one of the drug lumens or extruded into the catheter wall.

It will be understood that the embodiment in Figure 10 can be constructed without a drug recovery 25 lumen, if desired. Also, Figure 10 shows a guide wire lumen 11 which may be omitted, depending on the intended medical use of the device, such as urological applications.

The embodiment in Figure 11 illustrates a 30 further embodiment of a drug delivery apparatus including a selectively permeable microporous membrane which includes a phonophoretic driving force including a transducer 28'' which is connected by conductors 29'' shown in the conductor lumen 27''. As in the case of 35 Figure 10, the drug delivery apparatus in Figure 11 includes a drug delivery lumen 45'' and lumens for the guide wire and conductor 11'', 27''. It will be

understood that the guide wire and conductor can be optionally excluded depending on the intended use of the drug delivery apparatus.

Although the description of the preferred
5 embodiment and method have been quite specific, it is contemplated that various modifications could be made without deviating from the spirit of the present invention. For example, angioplasty and drug delivery through a perforated balloon may be simultaneously
10 performed to a localized area of coronary or peripheral arteries or any other type of body passage that has a stricture. Additionally, such a perforated balloon may be combined with iontophoresis or phonophoresis to drive the drug into or through the vessel wall. Further, a
15 drug can be delivered to an internal body tissue through a selectively permeable membrane portion of a drug delivery component connected to a catheter. Accordingly, it is intended that the scope of the present invention be dictated by the appended claims,
20 rather than by the description of the preferred embodiment and method.

WE CLAIM:

1. A method for simultaneously performing angioplasty and delivering a drug to a localized area of a passageway with a catheter having a proximal end and a distal end and a balloon operably connected to the distal end, the method comprising the steps of:
 - a) advancing the catheter through the passageway until the balloon is adjacent to the localized area;
 - b) injecting a fluid through an injection lumen in the catheter and into a chamber of the balloon causing the balloon to inflate and apply pressure against the localized area of the passageway thereby dilating the localized area of the passageway; and
 - c) transporting the drug to the localized area while simultaneously dilating the localized area of the passageway.
2. The method of claim 1 wherein the step of transporting the drug is performed while the localized area of the passageway is dilated.
3. The method of claim 1 wherein the drug comprises at least a portion of the fluid and further wherein the step of transporting the drug further comprises transporting the drug through a selectively permeable portion of the balloon.
4. The method of claim 3 wherein the step of transporting the drug through a selectively permeable portion of the balloon further comprises transporting the drug through a microporous membrane.
5. The method of claim 4 wherein the step of

transporting the drug through a microporous membrane further comprises passing the drug through pores in the microporous membrane that have a size between 0.05μ and 1.0μ .

5

6. The method of claim 3 wherein the step of injecting further comprises injecting fluid into the balloon until the fluid within the chamber exerts pressure on the balloon that is between 1 and 90 psi.

10

7. The method of claim 3 further comprising the step of withdrawing at least a portion of the fluid from the chamber through a recovery lumen.

15

8. The method of claim 7 wherein the step of injecting the fluid further comprises injecting the fluid into the chamber and withdrawing the fluid from the chamber at a rate that maintains the balloon in an inflated state.

20

9. The method of claim 8 further comprising the step of causing the fluid within the chamber to exert a pressure on the balloon that is between 1 and 90 psi.

25

10. The method of claim 9 wherein the step of transporting the drug through a selectively permeable portion of the balloon further comprises transporting the drug through a microporous membrane.

30

11. The method of claim 10 wherein the step of transporting the drug through a microporous membrane further comprises passing the drug through pores in the microporous membrane that have a size between 0.05μ and 1.0μ .

35

12. The method of claim 3 wherein the step of transporting the drug through a selectively permeable portion of the balloon further comprises phonophoretically transferring the drug through the selectively permeable portion of the balloon.
13. The method of claim 3 wherein the step of transporting the drug through a selectively permeable portion of the balloon further comprises iontophoretically transferring the drug through the selectively permeable portion of the balloon.
14. The method of claim 13 wherein the step of iontophoretically transferring the drug further comprises passing a wave form of electrical pulses through the selectively permeable portion.
15. The method of claim 1 further comprising the step of coating a portion of an outer surface of the balloon with a gel before the catheter is advanced through the passageway.
16. The method of claim 15 wherein the gel contains the drug and the step of transporting the drug to the localized area further comprises transferring the drug from the gel to the localized area of the passage.
17. The method of claim 1 further comprising the step of coating a portion of an inner surface of the balloon with a gel before the catheter is advanced through the passageway.
18. The method of claim 17 wherein the step of transporting the drug further comprises passing the fluid from the chamber, through the gel, and through a selectively permeable portion of the balloon.

19. A method for simultaneously performing angioplasty and delivering a drug to a localized area of a passageway with a catheter having a proximal end and a distal end, an outer balloon operably connected to the distal end, and an inner balloon that is within the outer balloon, the method comprising the steps of:
- a) advancing the catheter along the guide wire until the outer balloon is adjacent to the localized area;
 - b) injecting a drug through a first lumen and into a first chamber that is between the outer balloon and the inner balloon;
 - c) injecting a drug through a second lumen and into a second chamber within the inner balloon causing the inner balloon and the outer balloon to inflate thereby dilating the localized area of the passage; and
 - d) transporting the drug to the localized area.
20. The method of claim 19 wherein the step of transporting the drug is performed while the localized area of the passageway is dilated.
21. The method of claim 19 wherein the step of transporting the drug includes passing the drug through pores in a selectively permeable portion of the outer balloon, the pores having a size between 0.05 μ and 1.0 μ .
22. The method of claim 19 comprising an additional step of withdrawing at least a portion of the drug from the first chamber between the inner balloon and the outer balloon through a recovery lumen thereby circulating at least a portion of the drug from the first lumen, through the first chamber, and out the

recovery lumen.

23. The method of claim 19 wherein the outer balloon has a selectively permeable portion and the step of transporting the drug further comprises phonophoretically transferring the drug through the selectively permeable portion of the balloon.
24. The method of claim 19 wherein the outer balloon has a selectively permeable portion and the step of transporting the drug comprises iontophoretically transferring the drug through the selectively permeable portion of the balloon.
25. The method of claim 24 wherein the step of iontophoretically transferring the drug further comprises passing a wave form of electrical pulses through the selectively permeable portion.

FIG. 1

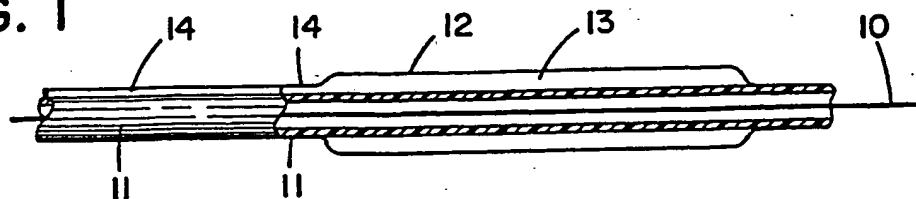


FIG. 2

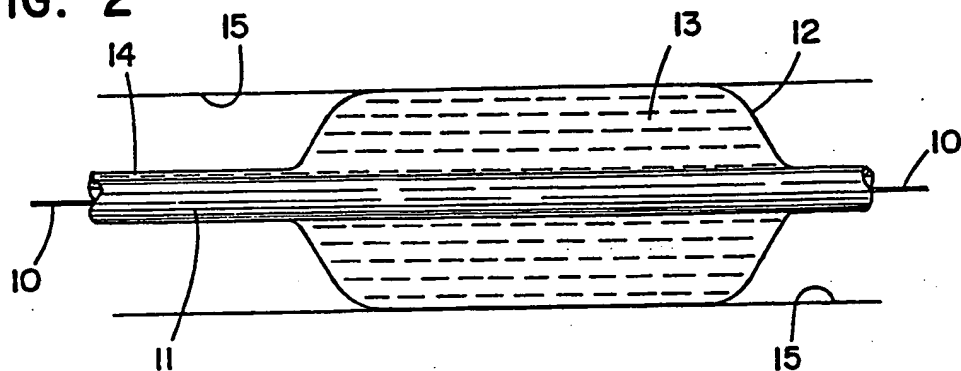


FIG. 3

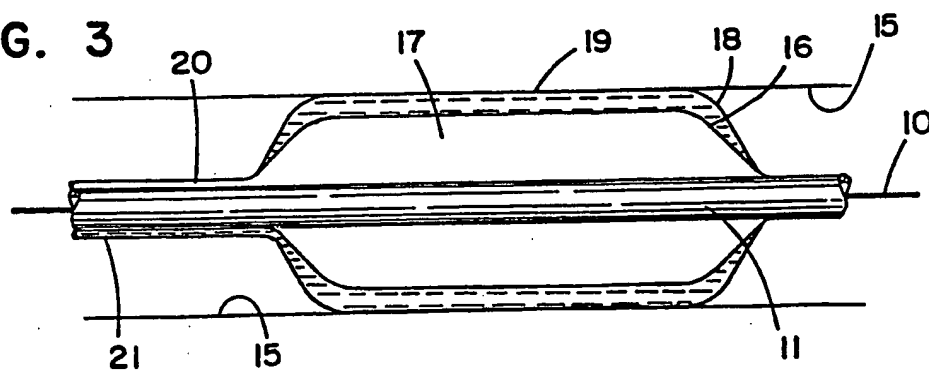
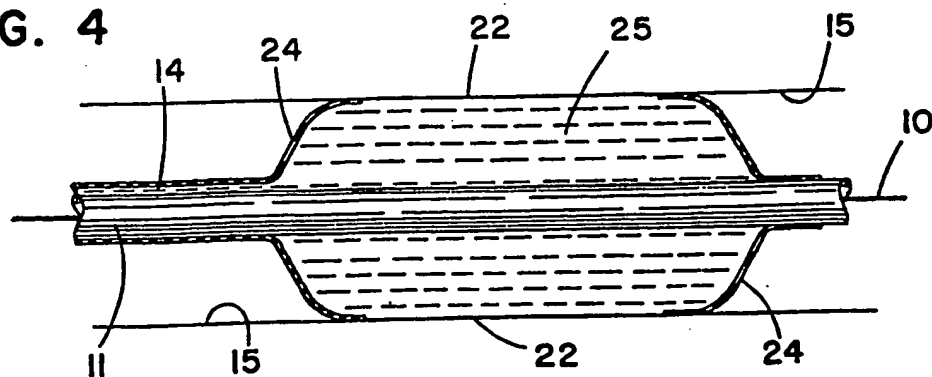


FIG. 4



2 / 4

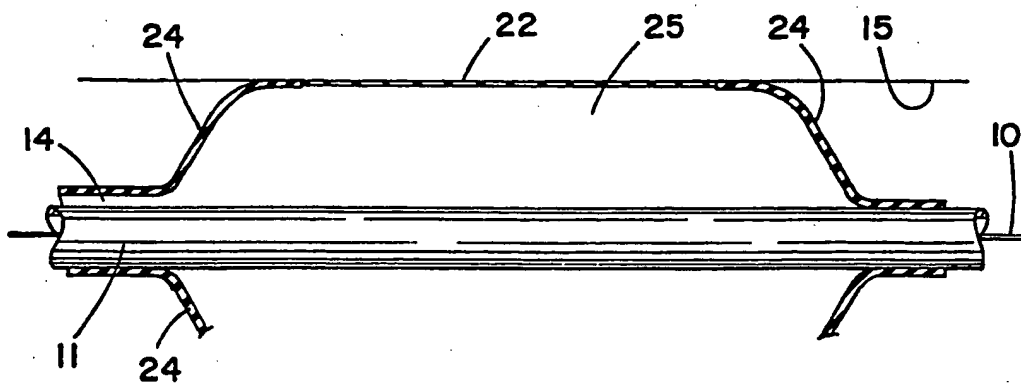


FIG. 5

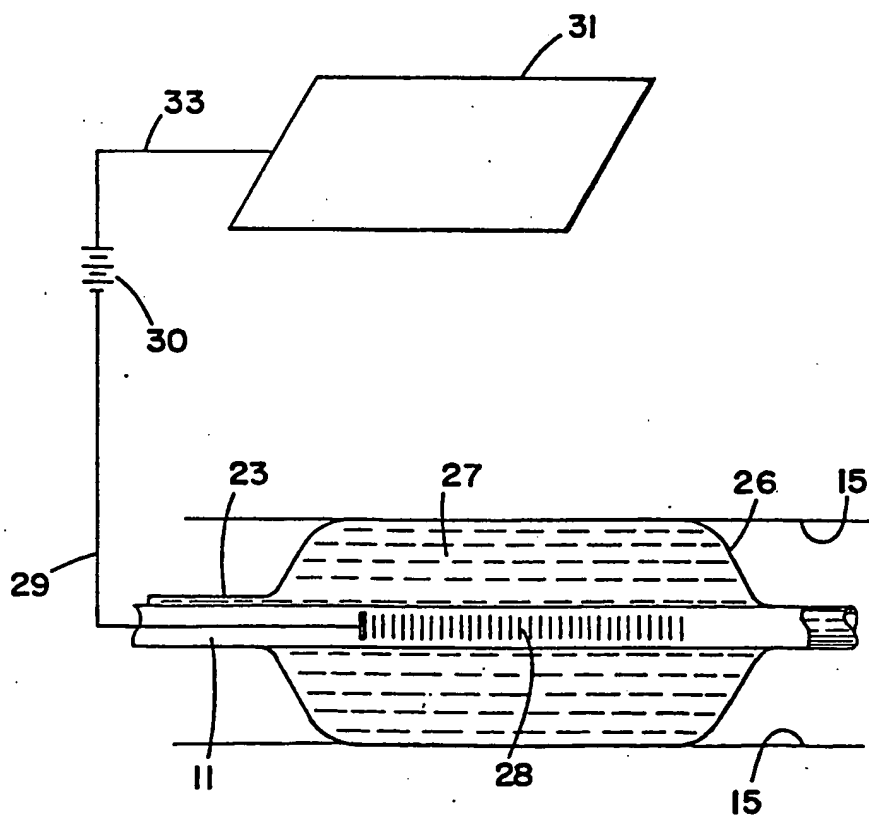


FIG. 6

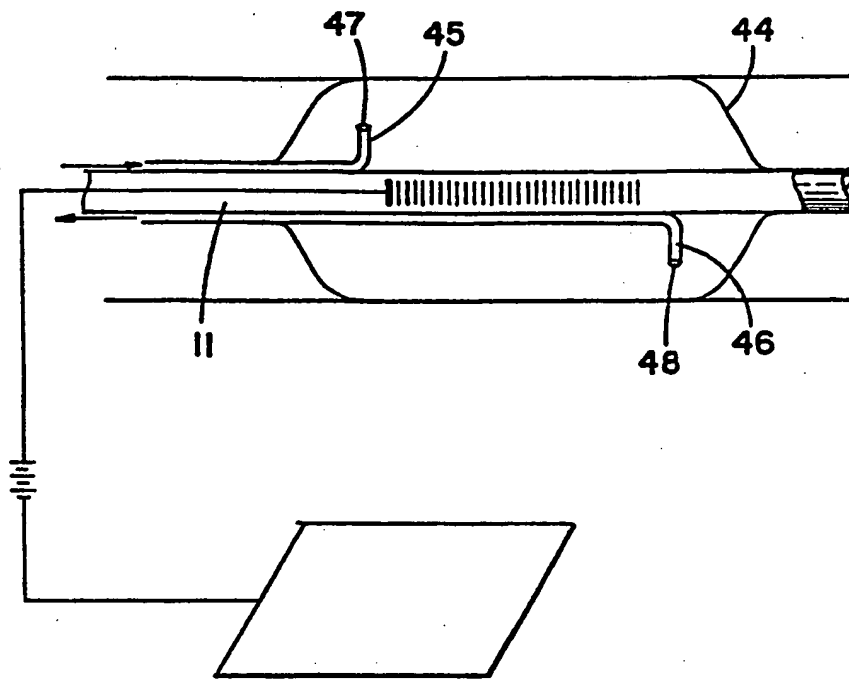


FIG. 7

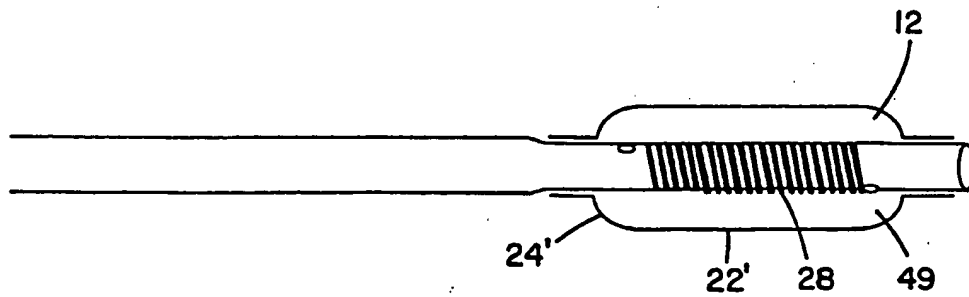


FIG. 8

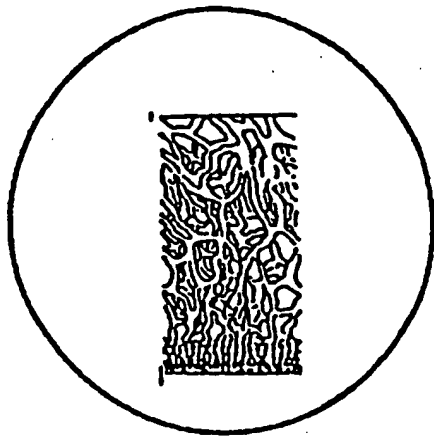


FIG. 9A

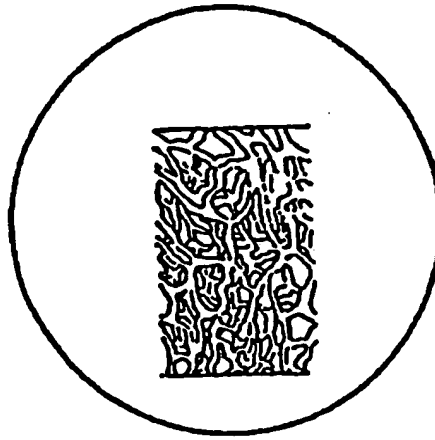


FIG. 9B

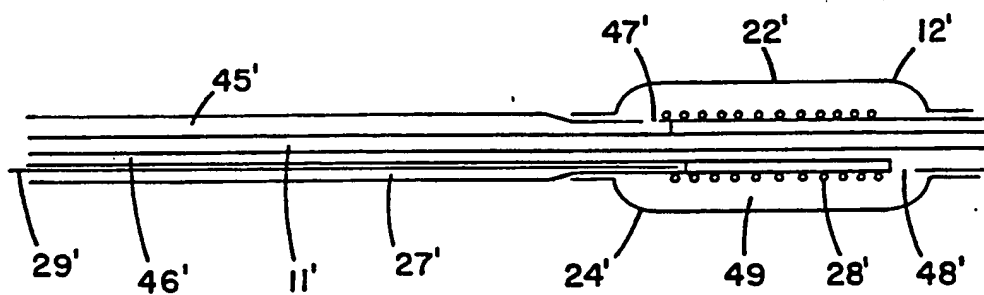


FIG. 10

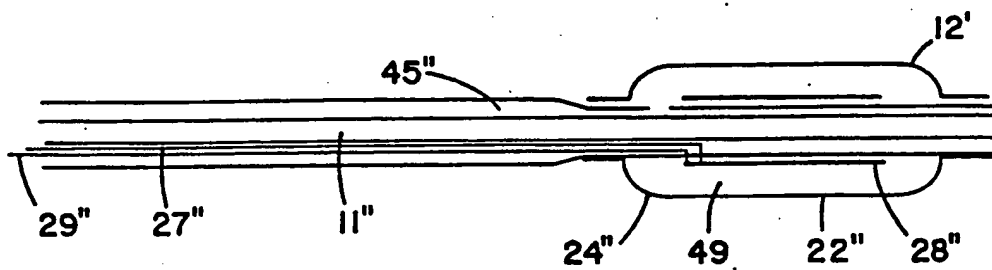


FIG. 11

INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/US 94/09590

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M29/02 A61M37/00 A61N1/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 19529 (CORTRAK MEDICAL INC.) 26 December 1991 see the whole document ---	
A	EP,A,0 399 712 (SCHNEIDER INC.) 28 November 1990 see column 2, line 23 - line 53 ---	
A	DATABASE WPI Section Ch, Week 8619, Derwent Publications Ltd., London, GB; Class A91, AN 86-121880 & JP,A,61 060 729 (NOK KK) 28 March 1986 see abstract -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

30 November 1994

Date of mailing of the international search report

08.12.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Schönleben, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/09590

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9119529	26-12-91	AU-A- 8074591	07-01-92
		EP-A- 0533816	31-03-93
		US-A- 5286254	15-02-94
		US-A- 5282785	01-02-94

EP-A-0399712	28-11-90	US-A- 4994033	19-02-91
		AU-B- 611077	30-05-91
		AU-A- 5595690	06-12-90
		CA-A- 2017319	25-11-90
		DE-U- 9005882	08-11-90
		DE-D- 69007674	05-05-94
		DE-T- 69007674	14-07-94
		ES-T- 2050370	16-05-94
		JP-C- 1777087	28-07-93
		JP-A- 3007169	14-01-91
		JP-B- 4064709	15-10-92

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/ 09590

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-25
because they relate to subject matter not required to be searched by this Authority, namely:
See Rule 39.1 (iv), method for treatment of the human body.
The search has been based on the alleged apparatus
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.